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Targeting cytokines to tumors to induce active antitumor immune responses by recombinant fusion proteins.

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Cytokines such as interleukin-2(IL-2), gamma interferon (IFN-gamma) and alpha tumor necrosis factor (TNF-alpha) are important mediators in immune responses against tumors. However, their therapeutic efficacy and clinical utilities in treatment of human malignancies are in large part limited due to the low concentrations of cytokine in tumors and the severe toxic side-effects derived from high-dose administration of cytokines. One critical issue to improve therapeutic efficacy is how to increase the local concentration of cytokine in tumors without causing severe side-effects. A series of recent reports demonstrated that the introduction of cytokine genes into tumor cells and subsequent local secretion can circumvent the limitations associated with the systemic cytokine administration. An alternative means of cytokine delivery is to target cytokines to tumor cells with tumor specific antibodies. Thereby, effective local cytokine concentrations can be achieved at the tumor sites without resorting to patient-specific therapy. With the advance in biotechnology, two structurally disparate domains of immunoglobulin and cytokine can be brought together into one fusion protein molecule by protein engineering. These engineered antibody-cytokine fusion proteins combine the unique targeting ability of tumor-specific antibodies with the multifunctional activity of cytokines. In general, there are two commonly engineered fusion proteins, the F(ab')₂/cytokine expressed in mammalian cells and the single-chain FV/cytokine expressed in *Escherichia coli*. Both the tumor-binding reactivity and the functional cytokine activity are maintained in most of fusion proteins. Therefore, these fusion proteins may be useful in targeting cytokine to tumors to stimulate immune destruction of tumors, while limiting severe toxic side-effects by the high dose of cytokine administration. Recent preclinical studies have shown that these fusion proteins are able to target cytokines to tumors expressing the tumor-associated antigen in vivo, and to inhibit both the primary and metastatic tumors in an immune competent animal model. Therefore, these recombinant fusion proteins may represent a new generation of novel immunotherapeutic reagents for the treatment of